REMARKS

The Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 10, 11-17, 18-21, 30 and 31 and have canceled claims 2, 4-9, and 22-29. Specifically, claim 1 has been amended to recite a double stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human HD nucleotide sequence, and wherein the double stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. Support can be found in the specification at, for example, pages 8, 9, 11, 16, 17, 55, 74, 79, and Tables I and II. Claims 3, 10, 11-17, 18-21, 30 and 31 have been amended to recite a double stranded nucleic acid molecule. Support for the amendment can be found throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO: 3578. The sequence represents GenBank entry NM_002111 (see Tables I and II). The version of NM_002111 appearing in the sequence listing as SEQ ID NO: 3578 appeared in GenBank on October 31, 2000. The sequence listing adds no new matter and applicants respectfully request its entry.

Rejection of Claims 13-15, 18 and 30 Under 35 U.S.C. § 112, second paragraph

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Claims 1-31 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants are not entirely certain of the basis for the rejection, it appears that the Office is suggesting that the claims require a recitation that the nucleic acid molecules comprise purine and pyrimidines. However, the structure of nucleic acid is well known, thus, Applicants submit that one skilled in the art would know that nucleic acid molecules contain purine and pyrimidine nucleotides and such recitation is not required. Claims 13-15, 18, and 30, as amended, have sufficient antecedent basis.

Applicant respectfully requests withdrawal of the 35 U.S.C. §112, second paragraph, rejection.

Rejection of Claims 36-69 Under 35 U.S.C. § 112, first paragraph

Claims 1-31 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 10, 11-17, 18-21, 30 and 31.

The Office Action asserts that although the specification as filed discloses siNA sequences targeted to HD, the specification does not provide information regarding what structure directs cleavage of any HD RNA via RNAi. The Office Action concludes that the skilled artisan would not be able to envisage the entire genus claimed of siNA molecules that would direct cleavage of any HD RNA. Applicants respectfully disagree with this argument, however, in the interest of expediting prosecution, claim 1 has been amended to remove the functional language "directs cleavage of a huntingtin (HD) RNA via RNA interference". Claim 1 as amended is directed to a double stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human HD nucleotide sequence, and wherein the double stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. The claim as amended is fully supported by the written description of the application as discussed in detail below.

Under 35 U.S.C. § 112, first paragraph, all that is required to satisfy the written description requirement is that the specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); M.P.E.P § 2163(I). Possession is shown "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. § 2163.02 (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir.1997)).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; and (5) the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient. *Id*; *see Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Contrary to the Office's allegation, the specification fully describes the claimed double stranded nucleic acid molecules in sufficient detail such that one skilled in the art would

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

reasonably conclude that applicants had possession of the claimed invention. For example, the specification teaches the structure, function, and properties of the target HD gene (specification at, for example, pages 122-124). Importantly, the specification provides the sequence of **numerous** exemplary HD target nucleic acid sequences (see HD sequences referred to by Genbank Accession numbers listed in Table I) and further teaches that the HD target includes other HD encoding sequences, such as other HD isoforms, mutant HD genes, splice variants of HD genes, and HD gene polymorphisms (see pages 8, 10, and 54).

In addition, the specification teaches the structure and chemical properties of the claimed double stranded nucleic acid molecules. First, the specification teaches that the double stranded nucleic acid molecule comprises a sense strand and an antisense strand (specification at, for example, pages 10-12, 21-25, and 70). The antisense strand comprises sequence complementary to human HD nucleotide sequence (which HD sequence is taught as discussed above). The sense strand comprises sequence complementary to the antisense strand. The specification further teaches that the size of the double stranded nucleic acid molecules is 18 to about 27 nucleotides in length (specification at, for example, pages 21, 22, and 34). Importantly, the specification teaches the structure, i.e., sequence, of **thousands** of representative examples of the claimed double stranded nucleic acid molecules (see Table II). In addition, the specification teaches that the double stranded nucleic acid molecules can be chemically modified and teaches **numerous** examples of various types of chemical modifications (specification at, for example, pages 13-49 and 99-108) and provides **numerous** examples of chemically modified double stranded nucleic acid molecules (see Table III and Figures 4 and 5).

In addition to teaching the structural, chemical, and physical properties of the claimed double stranded nucleic acid molecules, the specification teaches the functional characteristics of the claimed double stranded nucleic acid molecules, namely to modulate the expression of HD gene (specification at, for example, pages 49-54).

Finally, the specification teaches methods of making the claimed double stranded nucleic acid molecules (specification at, for example, pages 95-99, 124-126, and 130-132) and methods of testing the activity of the double stranded nucleic acid molecules (specification at, for example, pages 132-136). The specification also teaches the administrating the claimed double stranded nucleic acid molecules (specification at, for example, pages 108-122) and several uses of the double stranded nucleic acid molecules (specification at, for example, pages 137-139).

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Thus, the specification teaches virtually **ALL** of the characteristics listed in MPEP 2163(II)(A)(2)-(3)(a) used to demonstrate possession of the invention, as well as additional characteristics.

The Office argues that an adequate written description of a chemical invention requires the precise definition, such as by structure, formula, chemical name, or physical properties, and "not merely a wish or plan for obtaining the chemical invention claimed", citing Univ. of Rochester v. G.D. Searle & Co. However, the Searle case is distinguishable from the instant application for several reasons. First, applicants point out that the claims of the patent at issue in the Searle case were drawn to therapeutic methods (of selectively inhibiting the activity of PGHS-2), not to compound claims as in the instant application. Second, the Court determined that the method claims were invalid because the patentees had not described or provided a single example of a compound that selectively inhibits activity of PGHS-2. In sharp contrast to the Searle case, applicants provide numerous representative examples of double stranded nucleic acid molecules that target human HD sequences and teach the sequence, i.e., structure, of the exemplary molecules (see Table II). Applicants also provide the precise sequence and chemistry, including modified nucleotides, of numerous further representative examples of double stranded nucleic acid molecules that target human HD sequence (see Table III). Finally, the Searle case relates to a situation in which the potential compounds that may inhibit the activity of PGHS-2 could have widely divergent chemical structures, sizes, and physical properties and where the specification provides no teaching or guidance whatsoever as to possible common features between different structures. Such circumstances do not exist in the instant application in which all of the claimed molecules share common physical and structural properties, including comprising nucleic acid, having a double-stranded structure, having sequence complementarity to a human HD target (the sequence(s) of which is taught), and having a common size range of 18-27 nucleotides, and where these chemical and structural properties are clearly taught in the specification .

Despite the teachings and examples provided in the specification, the Office alleges that the applicants have not shown possession of the invention. In making the argument, the Office appears to allege that an applicant does not show possession unless he or she has reduced the invention to practice. However, applicants submit that the written description requirement does not require an actual reduction to practice. MPEP 2163 (II)(A)(3)(a). Thus, an applicant does

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

not have to include a working example to satisfy the written description requirement. Regardless, applicants submit herewith in Exhibit A a copy of Example 9 and Figure 30 which were filed with the corresponding continuation application USSN 11/063415, filed February 22, 2005. Example 9 and Figure 30 describe and show the results of experiments performed to test the activity of several of the double stranded nucleic acid molecules described in Table III of the instant application (see page 195). As explained in Example 9 and Figure 30, applicants tested the activity of double stranded nucleic acid molecules 31993/31994, 31995/31996 (chemically modified), and 31997/31998 (chemically modified) in HEK-293 cells and found that each of them inhibits the human HD target as compared with inverted matched chemistry control nucleic acid molecules.

Applicants have demonstrated possession of the claimed invention by providing the structure and chemistry of numerous representative examples of double stranded nucleic acid molecules that target HD (throughout the entire specification and in the Tables) and by demonstrating that exemplary double stranded nucleic acid molecules target and inhibit human HD.

Applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

Priority

The Office Action alleges that the instant application is not entitled to priority to International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/406,784, 60/408,378, 60/409,293, and 60/440,129. The Applicant respectfully disagrees.

The present application claims priority to, *inter alia*, 60/363,124 (the '124 application), filed March 11, 2002. The claims presented above all find support in, *inter alia*, the '124 application. The Office specifically alleges that although the prior applications disclose siNA molecules, they fail to discuss a siNA molecule that targets HD RNA. However, the '124 application teaches siNA molecules targeted to HD RNA in Table III of the application (entry in Table III for GenBank Accession No. NM_002111). Furthermore, in particular, amended claim 1 finds support for chemically synthesized double-stranded nucleic acid molecule at p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the first

and second strands at p. 12, lines 4-7, p. 19, lines 11-14, p. 20, lines 16-20, p. 21, lines 3-6, and p. 25, lines 17-29; one strand having between 18-27 nucleotides complementary to human HD nucleic acid sequence at p. 18, lines 1-5, p. 12, line 6, p. 372, entry in Table III for GenBank Accession No. NM_002111; and at least two different modified nucleotides at p. 5, line 13 to page 15, line 9, and p. 36, line 1 to page 37 line 31.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
3	One or more ribonucleotides: p. 15, lines 3-9
10	Sense strand connected to antisense strand via linker molecule: p. 19, lines 20-21, 25, 28, p. 20 line 15, p. 38 lines 17-29
11	Polynucleotide linker: p 12, lines 13-26, p. 38, lines 18-29
12	Non-nucleotide linker: p 12, lines 13-26
13	One or more pyrimidine nucleotides present in sense strand are 2'-O-methyl pyrimidine nucleotides: p. 10, lines 13, 27, p. 11, lines 8, 22
14	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
15	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
18	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
19	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 14-15
20	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
21	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25
30	Terminal phosphate group: p. 8, line 26 to p. 9, line 13
31	Composition comprising the double stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Therefore, the instant application is entitled to a priority date of at least March 11, 2002.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-9, 13-14, 19-20, and 23-31 stand rejected as allegedly obvious over Hayden *et al.*, (US 2002/0187931), Hammond *et al.*, (Nature, 2001), Elbashir *et al.*, (EMBO J, 2001), and further in view of Parrish *et al.* (Molecular Cell, 2000). Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 13-14, 19-20, 30 and 31.

The amended claims recite chemically synthesized double-stranded nucleic acid molecules comprising a sense strand and an antisense strand. Each strand of the double stranded nucleic acid molecule is 18 to 27 nucleotides in length. The antisense strand has complementarity to human HD nucleotide sequence and the sense strand has complementarity to the antisense strand. The double stranded nucleic acid molecule molecule further comprises at least two different modified nucleotides.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143..

Here, there is no suggestion or motivation to combine the cited references. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

An examiner can satisfy burden of the obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Hammond *et al.* is a general review article that discusses post-transcriptional gene silencing by double-stranded RNA. Hammond *et al.* fail to teach, mention, or suggest chemically modified double stranded nucleic acid molecules targeting a human HD nucleic acid sequence. Also, given that the nucleic acids discussed by Hammond *et al.* are long double stranded RNA (i.e. much longer than the presently claimed double stranded nucleic acid molecules), Hammond *et al.* fail to teach, mention, or suggest chemically modified double stranded nucleic acid molecules of length 18-27 nucleotides.

Parrish, too, fails to teach or suggest targeting a human HD nucleotide sequence. Importantly, Parrish et al fails to teach double-stranded nucleic acid molecules of length 18-27 nucleotides and, in fact, teaches away from double-stranded nucleic acid molecules of shorter size. While Parrish et al reports that duplexes as short as 26 bp can trigger RNAi (Abstract), Parrish *et al.* specifically demonstrates that dsRNA having only 23 uninterrupted nucleotides identical to the target have no RNAi activity whatsoever (p. 1079, right col. and Figure 3B). Thus, Parrish et al. teaches that siRNA must be at least 24 nucleotides in length to have RNAi activity. Furthermore, Parrish fails to teach any double stranded nucleic acid molecules having two different modified nucleotides.

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Elbashir *et al.* teaches siRNA technology generally, but fail to teach, mention, or suggest double stranded nucleic acid molecules targeting a human HD nucleotide sequence. Furthermore, Elbashir fails to teach any double stranded nucleic acid molecules having two different modified nucleotides.

Hayden *et al.* teach an antisense compound targeted to a HD gene but fail to teach, mention, or suggest double stranded nucleic acid molecules targeting a human HD nucleotide sequence. Hayden et al. is directed to antisense technology, not RNA interference. As antisense and RNAi involve completely different mechanisms (e.g., activity in the nucleus for antisense versus cytoplasm for RNAi; single-stranded requirement for antisense versus double-stranded for RNAi) and completely different biological cofactors (e.g., RNase H for antisense versus RISC complex for RNAi), the Office's implication that short interfering nucleic acid molecules can be merely substituted for antisense oligonucleotides is misguided. See, for example, Zamore et al., PLos Biology, 2:0465-0475 (2004) which clearly states that siRNA binding to target is distinct from simple complementary binding by antisense oligonucleotides (p. 0472, right column, second full paragraph).

Thus, even though short interfering nucleic acid molecules share a common characteristic with antisense oligonucleotides, namely that of binding to target nucleic acid, they have different structural and functional properties and operate via a completely different mechanism of action. For example, unlike the siRNA-mediated RNA interference process, antisense technologies do not operate via an endogenous mechanism, which accounts for the significant improvement in potency of siRNAs compared to the antisense oligodeoxynucleotides. Further, unlike the siRNA technology that involves a double-stranded RNA, the hallmark of the antisense technology is the use of a single-stranded DNA oligonucleotide. Antisense technology is a process whereby a single-stranded nucleic acid molecule hydrogen bonds to a targeted mRNA in the nucleus of the cell. The resulting single stranded antisense nucleic acid-mRNA duplex is degraded by a nuclease, RNAse H, in the cell nucleus, which theoretically would prevent the expression of the targeted gene. In contrast, siRNA-mediated RNA interference technology is a process whereby a siRNA molecule, which is at least partially a double stranded molecule, recruits a group of protein factors to form an RNA-induced silencing complex (RISC) predominantly in the cytoplasm of the cell. The siRNA-bound RISC complex is then directed towards the nucleic acid

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

sequence of a target mRNA that is complementary to one of the strands of the double-stranded siRNA to form siRNA-mRNA-RISC complex. The siRNA-mRNA-RISC complex then mediates cleavage of the bound mRNA in the cytoplasm of the cell thereby preventing translation of the encoded protein.

Given the structural and functional differences between antisense and siRNA technology, antisense involves different technology from RNA interference and constitutes non-analogous art. As such, a skilled artisan would have no suggestion to combine the references as the Office Action has done to target HD using double stranded nucleic acid molecules as presently claimed. While a suggestion need not be express in the prior art, it must be clear and particular; broad conclusory statements about the teachings of multiple references is insufficient. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000). The mere identification of a target (Hayden) and a general mechanism for suppressing expression (Elbashir and Parrish) without more is not the type of particularized suggestion necessary to sustain an obviousness rejection. The art must suggest the combination; it cannot come from the applicant's disclosure.[1]

The Office argues that Hammond teaches that "RNAi is a potent method", and further states that one would have been motivated "to use a dsRNA targeted to HD gene instead of an antisense because Hammond et al. teach using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies", (Office action page 7). However, because the dsRNA molecules taught by Hammond are long dsRNA molecules, one of skill in the art at the time of the instant invention would have been motivated to utilize the long dsRNA taught by Hammond rather than short dsRNAs as presently claimed. Furthermore, the motivation to utilize the longer dsRNA would have been supported by the teachings of Parrish, which would have generally taught away from the use of short dsRNAs as presently claimed because

[1] Indeed, the Board of Appeals made this very point in a non-precedential opinion (copy enclosed), holding that one publication's teaching of

a) general rules for the design of new RNA enzymes capable of highly specific RNA cleavage,
b) successful tests of these RNA against target sequences, and
c) the conclusion that provided that transcribed sequences of a gene are known it should be possible to target one or more ribozymes against specific RNA transcripts,

and a second publication's teaching of the TGF-β sequence did not establish a *prima facie* case of obviousness of a claim to an anti-TGF-β ribozyme absent a suggestion or motivation found in the prior art to combine the references. The Board warned that the knowledge cannot come from the applicant's disclosure.

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Parrish clearly shows that longer dsRNAs are more effective than short dsRNAs and, in fact, demonstrates that shorter dsRNAs do not have RNAi activity.

Claims 1-9, 13-14, 16-17, 19-20, and 22-31 stand rejected as allegedly obvious over Hayden *et al.*, (US 2002/0187931), Hammond *et al.,* (Nature, 2001), Elbashir *et al.,* (EMBO J, 2001), and further in view of Matulic Adamic *et al.* (U.S. Patent No. 5,998,203). Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 13-14, 16-17, 19-20, 30 and 31.

For the reasons previously stated above, Hayden *et al.*, Hammond *et al.,* and Elbashir *et al.,* do not teach the claimed nucleic acid molecules and furthermore there is no motivation to combine the references as suggested by the Office.

Matulic-Adamic fails to cure the deficiencies of the cited references. Matulic-Adamic teaches generally modifications of ribozymes. Thus, not only does Matulic-Adamic fail to teach, mention, or suggest the use of double stranded nucleic acid molecules, it fails to teach or suggest targeting human HD.

As with the antisense teachings of Hayden, Matulic-Adamic is not art the ordinary artisan would consider in making the claimed invention; it is non-analogous art. In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." In re Oetiker, 977 F.2d 1443, 1446, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992).

Matulic-Adamic (and Hayden) are simply not pertinent to the problem addressed by the presently claimed compounds, which is to provide double stranded nucleic acid molecules targeting human HD. Matulic-Adamic teach ribozymes (and Hayden teach antisense), both of which were known to modify RNA by mechanisms completely different and unrelated to RNAi. Despite the voluminous literature in the RNAi field, the applicants are unaware of a single instance in which a teaching regarding ribozymes or antisense has provided any insight into RNAi or been used in the study and development of double-stranded nucleic molecules that induce cleavage of target RNA by RNAi. Matulic-Adamic (and Hayden) are simply not references that would have commended itself to one of ordinary skill in the art in the

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

development of the presently claimed molecules or those of Elbashir or Parrish, which are not ribozymes or antisense molecules.

Claims 1-14, 19-20, 22 and 23-31 stand rejected as allegedly obvious over Hayden *et al.*, (US 2002/0187931), Hammond *et al.,* (Nature, 2001), Elbashir *et al.,* (EMBO J, 2001), and further in view of Schmidt et al., (Nucleic Acids Research, 1996) and Kennerdell et al., (Nature Biotechnology, 2000). Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 10-14, 19-20, 30 and 31.

For the reasons previously stated above, Hayden *et al.*, Hammond *et al.,* and Elbashir *et al.,* do not teach the claimed nucleic acid molecules and furthermore there is no motivation to combine the references as suggested by the Office. Neither Kennerdell nor Schmidt cure the deficiencies of the cited references. Kennerdell *et al.* provides teachings regarding gene silencing in *Drosophila* using dsRNA. The dsRNA, however, is several hundred base-pairs in length. Kennerdell provides no teachings regarding short double stranded nucleic acid molecules as presently claimed or HD as a potential target. Schmidt *et al.* provides teachings of hairpin ribozymes in which internal loop nucleotides essential to ribozyme activity are identified. Schmidt *et al.* provides no teaching regarding double stranded nucleic acid molecules as presently claimed or HD as a potential target.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316(Fed. Cir. 2000).

The priority date of the application is at least March 11, 2002. Therefore, as of March 11, 2002, it must be determined if one of ordinary skill in the art had a reasonable expectation of success in making a chemically modified double-stranded nucleic acid molecule comprising a

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

sense strand and an antisense strand, wherein each strand of the double stranded nucleic acid molecule is 18 to 27 nucleotides in length; wherein the antisense strand of the double stranded nucleic acid molecule comprises a nucleotide sequence that is complementary to a human HD nucleic acid sequence and the sense strand is complementary to the antisense strand; and wherein the double stranded nucleic acid molecule comprises at least two different chemically modified nucleotides.

In 2001 one of ordinary skill in the art knew:

1. That siRNA technology existed. *See,* Elbashir, Hammond and Parrish;
2. That antisense can be targeted to a HD transcript. *See,* Hayden;
3. That chemical modifications could be made to ribozymes. *See,* Matulic-Adamic.

One of ordinary skill in the art, as of March 11, 2002, would not have had a reasonable expectation of success of making a double stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human HD nucleotide sequence, and wherein the double stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. The cited references merely demonstrate that double stranded nucleic acid technology existed, that HD could be targeted with antisense, and that chemical modifications could be made to ribozymes which are distinct from the double stranded nucleic acid molecules of the invention. At the time of the invention, the successful use of chemically modified short double stranded nucleic acid molecules in mammalian systems was highly speculative at best. Importantly, the art did not recognize that modification with at least two different chemically modified nucleotides could be tolerated in double stranded nucleic acid molecules. Application of this technology to targeting human HD nucleotide sequence would not be envisioned by one of skill in the art with any reasonable expectation of success. Therefore, in the absence of any teaching whatsoever of a double-stranded nucleic acid molecule as presently claimed, one skilled in the art would have no reasonable expectation of success of making such molecule.

For the reasons set forth above, Hayden, Hammond, Elbashir, and Parrish, further in view of Matulic-Adamic, Schmidt and Kennerdell do not teach or suggest making a double stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

HD nucleotide sequence, and wherein the double stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides with a reasonable expectation of success and thus does not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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Anita J. Terpstra
Registration No. 47,132

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002